

## Opportunities and priorities for breast surgical research

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## Review

### Opportunities and priorities for breast surgical research

Ramsey I Cutress<sup>1‡</sup>, Stuart A McIntosh<sup>2‡</sup>, Shelley Potter<sup>3, 4‡</sup>, Amit Goyal<sup>5</sup>, Cliona C Kirwan<sup>6,7</sup>, James Harvey<sup>6,7</sup>, Adele Francis<sup>8</sup>, Amtul R Carmichael<sup>9</sup>, Raghavan Vidya<sup>10</sup>, Jayant S Vaidya<sup>11</sup>, Patricia Fairbrother<sup>12</sup>, John Benson<sup>13</sup>, Malcolm W R Reed<sup>14</sup> on behalf of the Association of Breast Surgery

Surgical Gap Analysis Working Group\*

<sup>1</sup>Faculty of Medicine and Breast Unit, University of Southampton and University Hospital Southampton, Tremona Road, Southampton, Hampshire, SO16 6YD, UK

<sup>2</sup>Centre for Cancer Research and Cell Biology, Queen's University Belfast, 97 Lisburn Road, Belfast, BT9 7AE.

<sup>3</sup>Bristol Centre for Surgical Research, Population Health Sciences, Bristol Medical School, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK

<sup>4</sup>Bristol Breast Care Centre, Southmead Hospital, Southmead Road, Westbury-on-Trym, Bristol, BS10 5NB, UK

<sup>5</sup>Royal Derby Hospital Uttoxeter Road, Derby, DE22 3NE, UK

<sup>6</sup>Division of Molecular and Clinical Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, M20 4BX, UK

<sup>7</sup>Nightingale Breast Unit, University Hospital of South Manchester, Wythenshawe Hospital, Southmoor Road, M23 9LT, UK Manchester, UK

<sup>8</sup>University Hospitals Birmingham, Mindelsohn Way, Birmingham, B15 2TH, UK

<sup>9</sup>Queens Hospital, Belvedere Road, Burton on Trent, DE13 0RB and University of Aston, Aston Triangle, Birmingham B4 7ET

<sup>10</sup>New Cross Hospital, Royal Wolverhampton Hospitals NHS Trust, Wednesfield Road, Wolverhampton, WV10 0QP, UK

<sup>11</sup>Surgical Interventional Trials Unit, Division of Surgery and Interventional Science, University College London, London W1W 7EJ

<sup>12</sup>Independent Cancer Patients' Voice

<sup>13</sup>Cambridge Breast Unit, Addenbrooke's Hospital Cambridge and University of Cambridge CB2 0QQ and School of Medicine, Anglia Ruskin University, Cambridge, UK.

<sup>14</sup>Brighton and Sussex Medical School, BSMS Teaching Building, University of Sussex, Falmer, Brighton, BN1 9PX, UK

‡Denotes joint first authors

\*Members of the Association of Breast Surgery Surgical Gap Analysis Working Group are PUBMED citable authors and are listed at the end of the manuscript.

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**Correspondence to:** Ramsey Cutress, Somers Cancer Research Building, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK;

Tel: (+44) 023 8120 6184

E-mail: r.i.cutress@soton.ac.uk

## ABSTRACT

**Background:** The Breast Cancer Campaign Gap analysis (2013) established breast cancer research priorities without specific focus on surgical research nor the role of surgeons. The majority of breast cancer patients encounter a surgeon at diagnosis or during treatment, thus surgical involvement in design and delivery of high-quality research to improve patient care is critical. This review aims to identify opportunities and priorities for breast *surgical* research to complement the previous gap analysis.

**Methods:** Research-active breast surgeons met and identified topic areas for breast surgical research which mapped to the patient pathway. These included diagnosis, neoadjuvant treatment, surgery, adjuvant therapy and special groups (e.g. risk-reducing surgery). Section leads were identified based on research interests with invited input from experts in specific areas, supported by consultation with the Association of Breast Surgery (ABS) membership and Independent Cancer Patients' Voice (ICPV). The document was iteratively modified until participants were satisfied that key priorities for surgical research were clear.

**Results:** Key research gaps were identified for each topic area including: (1) issues surrounding overdiagnosis and treatment; (2) optimising selection for neoadjuvant therapies and subsequent surgery; (3) reducing re-operation rates for breast conserving surgery; (4) generating evidence for the clinical and cost-effectiveness of breast reconstruction and mechanisms for evaluating novel interventions; (5) determining optimal axillary management, especially post-neoadjuvant treatment; (6) defining and standardising indications for risk-reducing surgery. Strategies for resolving these knowledge gaps are proposed.

**Conclusions:** Surgeons are ideally placed for a central role in breast cancer research and should foster a culture of engagement and participation in research to benefit patients and the NHS. Development of infrastructure and surgical research capacity together with appropriate allocation of research funding will be needed to successfully address the key clinical and translational research gaps highlighted in this analysis within the next two decades.

**Keywords:** breast cancer; surgery; review; gap analysis

## INTRODUCTION

Breast cancer is the most common malignancy in the UK and the second commonest cancer worldwide<sup>1</sup>. More than 53,000 new cases are diagnosed annually in the UK, with one in eight women affected at some point in their lives<sup>2</sup>. Breast cancer incidence continues to increase, and the disease constitutes a major public health issue with significant resource implications; estimates for healthcare costs per patient are in excess of £12,000 in the 15 months following diagnosis<sup>3</sup>. Identifying cost-effective treatments for breast cancer is therefore both a clinical and a research priority. Furthermore, significantly improved survival rates mean that long term post-surgical quality of life issues are increasingly important to patients.

In 2012, the Breast Cancer Campaign (BCC) facilitated a series of workshops with the aim of identifying gaps in knowledge and formulating strategies to address these. The resulting gap analysis<sup>4</sup> prioritised areas for breast cancer research; however, there was minimal focus on surgical research or the potential role of surgeons in effective design and delivery of studies.

Surgeons are uniquely placed for a pivotal role in breast cancer research. Most patients see a surgeon at diagnosis and the majority undergo surgery as primary treatment. Surgical engagement is crucial for identifying and recruiting patients to research at almost all stages of the treatment pathway. Involving surgeons in development of research strategies may optimise trial design, facilitate recruitment and ensure that trials successfully accrue to time and target.

Historically, the pioneers in changing treatment paradigms for breast cancer were surgeons but nonetheless the quality of much surgical research has been variable<sup>5</sup>. Less than 5% of all government healthcare research funding is currently spent on surgical projects<sup>6</sup>. The Royal College of Surgeons in the UK has recently invested in infrastructure to promote surgical research and secure additional funding<sup>7</sup>, aiming to improve quality and value of surgical research, enabling all surgeons to embrace research as a means of enhancing surgical practice and patient care.

The Association of Breast Surgery (ABS) has recognised the need to increase engagement with breast cancer research. The ABS Academic and Research (A&R) Committee was convened in 2014 with the aim of “enhancing care and outcomes for patients with breast disease through the promotion and support of (surgical) research and innovation”. A key intention was to identify areas where surgeons could make significant research contributions, complementing the BCC gap analysis. This paper outlines opportunities and priorities for breast surgical research highlighted by this exercise.

## METHODS

The ABS A&R committee comprises research-active breast surgeons, trainees and patient representation. The committee agreed key topics on which to focus this surgical gap analysis and convened a workshop in May 2016. Chosen topics map to the patient care pathway and are listed as follows: a) diagnosis b) neoadjuvant therapy c) surgical treatment of the breast and axilla (including reconstructive and oncoplastic surgery) d) adjuvant therapy e) risk-reducing surgery and f) special groups (elderly, young women; breast cancer in pregnancy, male breast cancer and survivorship). For the purpose of this review, “surgical research” was not confined to studies of surgical procedures or techniques; it also included areas relevant to surgical practice where surgeons could contribute to successful design, conduct and completion of breast cancer-related projects to complement the BCC gap analysis.

Section leads were identified based on individual interests and expertise, had responsibility for enlisting further experts in each area and were tasked with providing a summary comment of:

- existing knowledge
- key surgical research questions in each area
- proposed future research to address these gaps.

The document was iteratively modified until all contributors considered that key themes and research priorities had been identified. Consultation with ABS membership and Independent Cancer Patients’ Voice (ICPV) included presentation at the ABS Annual Conference in May 2017 and a survey, prior to preparation of the final document.

The Gap Analysis survey was developed by members of the A&R Committee (RIC, SMcl, SP and MWR) based on key gaps identified by section leads and contributing experts (Appendix 1). Respondents were asked to rate the importance of research gaps in four areas (diagnosis and assessment (n=5); neoadjuvant therapy (n=7); surgical management (n=5) and special groups (n=5) on a 10-point Likert scale from 1 (not important) to 10 (most important) and to identify any additional research gaps that should be included in the analysis.

The survey was circulated to the ABS membership by email and at conference and was open for six weeks between 15th May and 30th June 2017. E-mail reminders were sent on two occasions to optimise response rates. Survey Monkey software ([www.surveymonkey.com](http://www.surveymonkey.com)) was used for data collection.

All responses were summarised using simple summary statistics. Thematic analysis of free-text was used to explore whether any key gaps had been omitted.

## RESULTS

A provisional document for consultation including 22 proposed research gaps was developed with input from 35 research-active surgeons and invited experts (ABS Gap Analysis Working Group, appendix 2). The ABS Gap Analysis survey was completed by 40 additional ABS members, 98% (n=39) of whom felt that there were gaps in breast surgical research that would benefit from additional research. All 22 identified gaps received a median score of between 7 and 9 and so all were retained. No additional gaps were identified, although reference was made to some gaps discussed in the 2013 BCC analysis. Consistent with our stated aims these have not been reiterated here. The principal surgical gaps identified are summarised in Table 1 and discussed below.

## DIAGNOSIS AND ASSESSMENT

### *Screen-detected breast cancer*

Approximately one third of breast cancer cases in England present through the National Health Service Breast Screening Programme (NHSBSP)<sup>2</sup> and addressing overdiagnosis (defined as detection of cancers that would never have been found were it not for the screening test) and overtreatment of

screen-detected breast cancer has been identified as a research priority in a recent independent review<sup>8</sup>.

### *Addressing overtreatment*

Surgeons have a key role in screening studies as traditionally they have been responsible for excision of screen-detected lesions. Use of vacuum-assisted biopsy (VAB) to obtain larger samples for histological assessment has replaced excision biopsy for many women with 'B3' lesions (of uncertain malignant potential)<sup>9</sup> but lack of randomised evidence has prevented universal uptake of the technique. The natural history of some B3 lesions (e.g. lobular carcinoma in situ (LCIS), flat epithelial atypia (FEA), and atypical ductal hyperplasia [ADH]) remains uncertain, and RCTs are required to determine the optimal management of indeterminate lesions.

Whilst there is agreement (albeit without supporting randomised evidence) that high-grade ductal carcinoma in situ (DCIS) requires surgical intervention, there is more uncertainty regarding management of low and intermediate grade DCIS<sup>10</sup>. LORIS (Low Risk DCIS) is a phase III trial comparing active monitoring with surgery for patients with screen-detected low risk DCIS, with the primary end-point being development of ipsilateral invasive breast cancer. The non-inferiority design aims to demonstrate whether active monitoring is not inferior to standard surgery in this group of women<sup>11</sup>. Similar studies are underway worldwide<sup>12 13</sup>, and translational studies to identify candidate biomarkers of disease progression are integral to these trials.

### ***Symptomatic breast cancer***

#### *Streamlining referral and diagnostic pathways for symptomatic breast patients*

Over half of breast cancers are diagnosed in symptomatic clinics following triple assessment<sup>14-16</sup> although over 90% of patients presenting to symptomatic breast clinics do not have cancer<sup>17</sup>. Alternative assessment methods, including radiology-led triple-assessment services or primary care open access schemes, may be more cost-effective than the current model, but require robust evaluation to demonstrate acceptable sensitivity, specificity and reliability before introduction.

### ***Advanced and emerging breast imaging modalities***

Research is needed to establish the role of breast magnetic resonance imaging (MRI) for specific scenarios such as assessing operability, clarifying local extent and planning complex breast conserving surgery<sup>18</sup>, as well as determining which patient groups may benefit from imaging with novel modalities such as contrast-enhanced mammography and digital breast tomosynthesis<sup>19</sup>. More sophisticated imaging may result in increased detection of previously subclinical ipsi- and contralateral breast lesions, mandating further radiological and pathological evaluation and potential excision<sup>20</sup>. There is a need to elucidate the clinical/biological significance of such lesions, and the impact of occult multifocality/multicentricity on oncological outcomes, to determine whether such small, previously subclinical lesions require surgical intervention. Furthermore, the impact of detecting and investigating subclinical disease on psychological well-being of women warrants further investigation.

### ***Staging investigations***

Staging investigations for distant metastases are not routinely recommended for asymptomatic patients presenting with breast cancer. Current practice is variable<sup>21</sup> and treatment decision making when lesions of uncertain clinical significance are identified can be challenging. Studies are needed to determine the most appropriate strategies and imaging modalities for staging and monitoring equivocal lesions.

## **MANAGEMENT**

Management of breast cancer is multimodal and the BCC gap analysis<sup>4</sup> recognises the need for a more personalised approach. Several areas of controversy relate to optimal selection and sequencing of treatment strategies in the neoadjuvant setting, including tailoring and sequencing local therapies (surgery and radiotherapy) after primary systemic therapy, and the potential role and outcomes of response-adapted surgery.

### ***Neoadjuvant therapy***

Neoadjuvant therapy is an established option in management of locally advanced breast cancer<sup>22</sup>, and can downsize larger cancers, permitting breast conservation. Neoadjuvant chemotherapy (NAC) is as effective as adjuvant chemotherapy in terms of overall survival for patients with operable cancer<sup>23-26</sup>. It allows disease down-staging, thereby potentially reducing the extent of surgery, although this may be



associated with increased rates of local recurrence, the reasons for which are unclear and warrant further investigation<sup>23</sup>. Neoadjuvant endocrine therapy (NET) is an alternative to NAC in women with oestrogen receptor positive (ER+) breast cancer, and further work is needed to establish the optimal duration of treatment<sup>27</sup>. Combination therapies (e.g. CDK4/6 inhibitors with aromatase inhibitors) may increase response rates, and are currently being explored in ongoing studies. There is less randomised evidence to support NET than for NAC in terms of impact on long-term survival. Of note, the POETIC trial demonstrated that response to short-term pre-operative aromatase inhibitor therapy did not impact time to recurrence<sup>28</sup>.

#### *Identifying patients who may benefit from neoadjuvant therapy*

Benefits of NAC in certain disease subgroups are well-established, with pCR rates of up to 50% seen in triple negative breast cancer with some regimens<sup>29</sup>. In HER2-positive disease, dual targeting with anti-HER2 therapies combined with chemotherapy can further increase pCR rates<sup>30,31</sup>. A meta-analysis did not confirm pCR to be a surrogate for improved overall survival<sup>32</sup>, although pCR at an individual patient level was prognostic. However, improved ability to identify patients likely to respond favourably to neoadjuvant therapies remains a key research focus and will guide clinical decision-making on sequencing of chemotherapy and surgery.

The optimal selection of neoadjuvant therapy (NAC or NET) in post-menopausal patients with ER positive disease remains to be determined. The role of molecular assays has yet to be fully elucidated<sup>33</sup> although early results with the 21 gene assay suggest possible clinical utility<sup>34</sup>. Likewise, a 4-gene signature has recently been proposed to allow patients to be classed as likely long-term responders or non-responders within 2 weeks of starting endocrine therapy<sup>35</sup>. Further high-quality prospective evidence is necessary to determine the value of such biomarkers.

#### *Monitoring response to neoadjuvant therapy*

Response can be assessed either clinically or radiologically and improved techniques for detection of early response may permit treatment strategies to be adjusted in non-responders (e.g. change of neoadjuvant regimen or proceed to surgery)<sup>36</sup>. Accurate prediction of response may increase the reliability of surgical decision-making when evaluating potential down-staging for breast conservation. Techniques to optimise monitoring of response may include novel imaging modalities, e.g. drug-induced

apoptosis has been described as a possible functional imaging technique in this context<sup>37</sup>. Further validation will however be required before such approaches can be utilised in the clinical setting.

#### *Management of patients with a complete pathological response in the breast*

The necessity for surgery in patients achieving pCR following neoadjuvant treatment remains to be addressed, and robust minimally-invasive methods to confirm pCR prior to surgery are needed. The NOSTRA trial aims to address this question by examining the need for surgery in HER-2 positive patients achieving pCR following combination NAC and dual anti-HER-2 therapy. In the feasibility phase all patients will undergo surgery, to determine whether patients with a pCR can be identified pre-operatively with multiple ultrasound-directed tumour-bed biopsies. In the main trial, patients with apparent pCR will be randomised to either surgery and radiotherapy or radiotherapy alone. This trial may demonstrate that surgery can be safely omitted in selected patients where the absence of residual disease can be accurately and reliably identified. Long-term follow-up will clearly be essential to monitor outcomes. Similar studies are ongoing internationally to address this question<sup>38</sup>.

#### *Management of the axilla in patients undergoing neoadjuvant chemotherapy*

Two key questions remain to be resolved in management of the axilla in the context of NAC: the timing of SLNB in patients clinically and radiologically node-negative at diagnosis, and the surgical management of patients who are initially biopsy-proven node-positive, but apparently convert to node-negative status following NAC.

In patients node-negative at presentation, current options are SLNB pre-treatment, or following NAC. Upfront SLNB potentially overtreats patients with subclinical nodal involvement which may be downstaged by NAC, as positive pre-treatment SLNB usually commits a patient to additional axillary treatment (surgery or radiotherapy). Between 40%-75% of patients with axillary metastasis at diagnosis become node negative following NAC, raising the possibility of post-treatment SLNB in this group. Two prospective cohort studies<sup>39,40</sup> have demonstrated high false negative rates in this setting. The sensitivity of SLNB was acceptable when post-treatment, nodes reverted to normal morphology on ultrasound, dual localisation techniques were used and a minimum of 3 nodes retrieved. The use of pre-treatment techniques for marking positive axillary lymph nodes prior to neoadjuvant therapy may improve accuracy by allowing targeted axillary dissection in this setting. This has been described using

a variety of methods including radioactive iodine seeds and clipping of positive node(s)<sup>41-43</sup> but these approaches require further evaluation and the question remains whether SLNB alone is safe in this setting, where there is potential risk of residual chemo-resistant axillary disease

With respect to neoadjuvant treatments, in the first instance, improved data are required to understand real world rates of conversion to breast conservation, change of chemotherapy regimen due to non-response, early abandonment of NAC in favour of early surgery, pCR rates, long-term local recurrence rates and overall survival.

### **Window of opportunity studies**

Window of opportunity (WoO) studies utilise the short time interval between diagnosis and surgery to examine biological effects of novel treatments in the *in vivo* setting. Window studies can:

- a) demonstrate, confirm or validate (proposed) biological mechanism(s) of action
- b) identify resistance or sensitivity profiles pre- and post- treatment
- c) identify surrogate endpoints that may correlate with long-term outcomes (such as changes in specific biomarkers seen in biopsies at diagnosis and at surgery)

They require a fraction of the time, cost and patient exposure to test therapies, compared with adjuvant trials. The “post-neoadjuvant window” between completion of neoadjuvant chemotherapy and surgery in those patients who fail to respond completely to treatment represents a further novel therapeutic opportunity which has yet to be exploited. Repeat tumour biopsy at conclusion of treatment can be used to identify patients with residual disease who might be suitable for targeted therapies during this timeframe.

WoO studies may provide an evidence base for proceeding to phase III trials. Surgeons have a role in the design and delivery of such trials. Involving patient advocates is also vital to allow concerns surrounding the acceptability of such studies to be addressed. Examples include reassurance to research ethics committees regarding tissue collection pre-treatment and open discussion of the effects of trial participation on scheduling of surgery. For practical purposes, trial entry counts as treatment for the purposes of meeting health service waiting time targets<sup>44</sup>.

## **Surgery for breast cancer**

### ***Surgery to the breast***

#### *Strategies to improve breast conserving surgery and to reduce re-excision rates*

Surgical resection margins remain contentious, but there is broad consensus that a negative margin, regardless of extent, is key to reducing local recurrence for invasive disease<sup>45</sup>. Currently, one in five women require further excision because of involved resection margins<sup>46</sup>. This represents a significant burden for patients and healthcare providers, and strategies to reduce margin positivity are a research and clinical priority.

#### *Intra-operative margin assessment*

Technologies allowing intra-operative margin assessment offer further potential to reduce re-excision rates beyond routine specimen radiology<sup>47</sup>. Intra-operative margin assessment techniques including imprint cytology and frozen section have not become routine practice due to resource limitations<sup>48</sup>. Emerging technologies for margin assessment potentially offer rapid and reliable methods for reducing rates of margin positivity. These include the MarginProbe (radiofrequency reflection)<sup>49</sup>, ClearEdge<sup>50</sup> (bio-impedance spectroscopy), and LightPath (Cerenkov Luminescence Imaging<sup>51</sup>). Other technologies such as Raman Spectroscopy<sup>52</sup> and the iKnife Rapid Evaporative Ionisation Mass Spectrometry technology<sup>53</sup> are also being explored, Feasibility and validation studies are required for all these technologies to determine clinical utility and cost-effectiveness. Surgeon-led multi-centre trials are necessary for comparison of newer technologies with current margin assessment techniques. This in turn will determine relative impact on re-excision rates.

#### *Tumour localisation for non-palpable lesions*

The ideal localisation method should be safe, accurate, deliverable in advance of the planned operation date and cost-effective. New approaches to localisation include use of radioactive<sup>54</sup> and magnetic seeds<sup>55</sup>. These may offer benefits over standard wire-guided techniques and are being validated in on-going studies with promising early results<sup>56,57</sup>. However, magnetic seeds limit subsequent use of MRI for imaging unless completely removed, and further evaluation is essential before comparative studies can be undertaken.

Surgeons have clear responsibilities in trialling new devices and participating in adequately powered prospective collaborative studies to validate novel localisation techniques. The current European approach to device testing involves CE marking of the device with no regulatory requirement for post-market research. A coordinated approach mandating prospective data collection (post-CE marking) for new devices is necessary, and working closely with the Medicines and Healthcare products Regulatory Agency (MHRA) and equivalent international bodies to ensure more robust assessment and evaluation may be one way to achieve this.

#### *Alternatives to surgical excision*

Standard surgical excision may be unnecessary for small, low-grade screen-detected cancers for which percutaneous ablation techniques such as cryotherapy, radiofrequency ablation, high-intensity focused ultrasound and laser therapy may be appropriate. However, techniques that completely ablate cancers<sup>58,59</sup> raise concerns about margin assessment and definitive histopathology. Hence percutaneous excisional techniques to remove tumours may be preferable in this respect. Further research will clarify which cancers are amenable to treatment with minimally-invasive techniques<sup>60-62</sup>, who requires adjuvant radiotherapy, and what constitutes adequate axillary management for individual patients.

Appropriate end-points for de-escalation studies need to be clearly defined and include local or regional recurrence, disease-free and overall survival. Designing studies which provide definitive data may pose significant methodological challenges. Randomised controlled studies with non-inferiority design are the gold standard but may be challenging due to patient and clinician preferences in non-blinded studies. Large cohort or patient preference studies may be more acceptable in this context. Multidisciplinary working, alongside patient advocates, will be necessary to define appropriate end-points and deliver well-designed studies that address these key questions.

#### *Adjuvant radiotherapy*

Adjuvant radiotherapy is an integral part of loco-regional therapy and reduces local recurrence. Intra-operative radiotherapy may safely reduce the burden of treatment on the patient and enable more

accurate targeting of tissues at risk<sup>101</sup> and the ongoing TARGIT-B trial will provide further data on potential benefits of this approach in terms of local tumour control and adverse effects. Avoidance of radiotherapy may be possible in some patient groups, particularly in light of the findings of the CALGB 9343 trial, which has confirmed low rates of ipsilateral recurrence at 10 years in patients  $\geq 70$  years of age with hormone receptor positive node negative tumours under 5cm treated with adjuvant hormone therapy alone after wide local excision<sup>63</sup>. This question is being addressed by the ongoing PRIMETIME study<sup>64</sup>.

### *Breast reconstruction and oncoplastic surgery*

Breast reconstruction is offered to improve cosmesis, body image and quality of life for women undergoing mastectomy<sup>65</sup>. Many reconstructive options are available, from implant-based techniques to autologous procedures. These can be performed at mastectomy or a later date. Decision-making for breast reconstruction can be complex, with reports of dissatisfaction and regret not uncommon<sup>66,67</sup>. Decision aids may reduce decisional conflict and increase knowledge about options<sup>68</sup> but these must be based on high-quality evidence.

High-quality patient-centred short and long-term outcome data for different reconstructive techniques are currently lacking<sup>69,70</sup>. Inconsistent and heterogeneous reporting of outcomes precludes comparison of results from different studies and there is an urgent need for a robust set of standardised outcomes, allowing comparisons across studies. Therefore, a core outcome set has been developed<sup>71</sup>, which includes 11 clinical, patient-reported and cosmetic outcomes important to both patients and healthcare professionals. Agreement regarding how to measure these outcomes is important before effective integration into research and clinical implementation. Development of a simple, reliable and valid method for assessing cosmetic outcomes of breast reconstruction is ongoing and includes use of three-dimensional imaging techniques<sup>72</sup>. Furthermore, inclusion of patient reported outcomes should be standard in all future research and well-validated tools are required for this purpose. One such tool is the BREAST-Q<sup>73,74</sup>, which is comprehensive, includes domains for breast satisfaction together with psychosocial and sexual well-being and is finding universal application.

The incidence of multifocal and multicentric cancers has increased with MRI usage and screening. Despite limitations of studies addressing surgical treatment of multiple ipsilateral breast cancers, rates of local recurrence are low after oncoplastic breast conserving surgery with no survival detriment. This has prompted the first randomised trial evaluating therapeutic mammoplasty versus standard mastectomy for these cases<sup>75</sup>.

With broadening indications for postmastectomy radiotherapy<sup>76</sup> (PMRT), further research is required to determine how to integrate radiotherapy into management plans to minimize surgical complications and adverse cosmetic outcomes in breast reconstruction<sup>77,78</sup>. A well-designed randomised trial addressing this issue has previously failed to recruit<sup>79</sup> however a recent survey of European practice confirms that there remain controversies around the scheduling of PMRT in the context of reconstructive surgery<sup>80</sup>. This question will be in part addressed by the PRADA trial (<https://clinicaltrials.gov/ct2/show/NCT02771938>), which is a non-randomised phase II trial exploring whether radiotherapy before mastectomy and autologous breast reconstruction is associated with improved aesthetic results without increasing post-operative complications secondary to upfront radiotherapy. Data from this study is awaited, although further research is required to resolve these issues and non-randomised studies with standardised outcome measures may be a pragmatic wayforward.

The optimal approach to implant-based breast reconstruction is another area of controversy. This is a rapidly evolving area and it is unclear what type of biological or synthetic mesh should be used and whether implants should be placed in the subpectoral or pre-pectoral plane. RCTs are challenging but the iBRA (implant Breast Reconstruction evAluation) study<sup>81</sup> (ISRCTN37664281) has prospectively recruited over 2000 patients undergoing new approaches to implant-based reconstruction at 81 centres to inform the feasibility and design of a future trial.

New surgical techniques must be prospectively evaluated using robust methodology. There should be “no innovation without evaluation” and infrastructure should be in place to support the introduction of new procedures and devices in a controlled and monitored fashion, encouraging more efficient innovation whilst protecting patients. The IDEAL framework<sup>82</sup> provides a methodology for achieving this. Adoption of innovation can be improved by collaborative approaches, linked to a network of high-volume centres willing and able to evaluate new devices and techniques. Engagement of industry and

regulators, as well as surgeons, in post-market surveillance of medical devices will be essential to deliver these innovation programmes in a timely and cost-effective fashion. Some aspects of best practice for devices and implants may be developed from regulatory processes for new medicinal products. Furthermore, in order to embed best practice in the context of complex procedures such as implant-based breast reconstruction, an improved understanding of the nature of adoption and implementation of such practice is necessary.

### **Management of the axilla**

Management of the axilla has become increasingly conservative and high-quality imaging may in future replace SLNB in patients with low-risk cancers. The SOUND trial (Sentinel node versus Observation after axillary UltraSound)<sup>83</sup> aims to address this, and recent work suggests this approach may be safe in selected patients<sup>84</sup>. In addition, with increasing numbers of patients having SLNB, the feasibility of repeat SLNB in patients with local recurrence and optimal management of the axilla following isolated regional nodal recurrence needs to be addressed.

#### *Patients with low volume nodal disease found by sentinel node biopsy*

There is continued controversy over treatment of sentinel node macrometastases. ACOSOG Z0011 challenged the therapeutic benefit of ANC for this patient group. However, these findings have not been readily adopted into clinical practice in the U.K. This may in part be due to the fact that Z0011 did not include mastectomy patients, and that half of patients received high tangent radiotherapy fields which may have favoured equivalence of outcomes. Recent updated analysis at 10 years<sup>85</sup>, confirming no significant difference in recurrence or survival, may go some way to addressing these concerns. The POSNOC trial<sup>86</sup> is exploring management of sentinel node macrometastases in both BCS and mastectomy patients, and will accrue 1900 patients, potentially providing more definitive answers on the safety of SLNB alone for patients with sentinel node macrometastases receiving adjuvant systemic therapies. Finally, the benefit of axillary dissection in patients with a clinically negative but needle biopsy positive axilla remains to be elucidated – these patients are eligible for entry into POSNOC and this may provide data to guide the management of this patient group.



Further advances in imaging technologies, percutaneous sampling techniques and systemic therapies for breast cancer may be forthcoming, and there is potential for elimination of surgical staging of the axilla in selected patients with node-negative and possibly some cases of node-positive disease.

## **SPECIAL GROUPS**

### ***Patients at high risk***

#### **Risk-reducing surgery**

##### *Management of women with a strong family history but no identified genetic mutation*

The surgical management of high-risk women with germline BRCA mutations is well-established, with bilateral risk-reducing mastectomy achieving a significant reduction (>90%) in breast cancer incidence<sup>87</sup>, although survival benefit remains unproven<sup>88</sup>. The optimal management of women with a strong family history of breast cancer but no identifiable mutation in a predisposition gene remains unclear, with no consensus about when (or if) risk-reducing surgery should be offered. Surgical intervention is not without risk and may include adverse psychosocial sequelae, decisional regret and dissatisfaction<sup>89</sup>. Well-designed studies using validated instruments for patient reported outcomes are lacking. Surgeons are often approached directly about risk-reducing surgery and are ideally placed to explore these issues alongside patients and psychologists.

##### *Contralateral prophylactic mastectomy*

Rates of contralateral prophylactic mastectomy (CPM) are increasing and more patients with unilateral breast cancer are requesting contralateral surgery with or without reconstruction either at initial diagnosis or subsequently<sup>90</sup>. There is no clear evidence for survival benefit for CPM<sup>91</sup> in the absence of a genetic predisposition. Despite recent guidelines<sup>92</sup>, there is no consensus for optimal management of this group<sup>93-95</sup>. There is a need to explore relative benefits and harms of CPM with accurate reporting of complications, long-term sequelae and validated patient-reported outcomes. Work to improve the effective communication of the competing risks (recurrence from the index primary and development of a new primary) will also be important to help with these complex decision-making processes and allow women to make fully informed choices.

#### **Surgery for metastatic disease**

A randomised trial<sup>96</sup> found no survival benefit from excision of the primary tumour in patients with metastatic disease. In the context of improved systemic and biological therapy for certain tumour subgroups, however, further research is required to identify specific patient subgroups which may benefit from excision of the primary tumour (such as those with isolated bone metastases<sup>97</sup> or with complete resolution of distant disease), and how this might impact on quality of life.

Further work is also needed to establish the magnitude of survival benefit from resection of breast cancer metastases. Non-randomised studies suggest that in selected patients, resection may be associated with significant survival benefit<sup>98,99</sup> but RCTs are needed to definitively establish the value of this approach. Other treatment modalities including stereotactic radiotherapy, radioablation and cryoablation of metastatic lesions require robust clinical evaluation.

### **Surgery for lymphoedema**

Lymphoedema following axillary surgery is disabling and adversely impacts quality of life. Surgery such as lymphaticovenous anastomosis and vascularised lymph node transfer may significantly improve outcomes for patients with severe symptoms<sup>100</sup> but further research is required to evaluate both the safety and effectiveness of these techniques and determine which patients derive symptom benefit while minimising donor site morbidity<sup>101</sup>.

### **Young women**

Management of breast cancer in young women presents specific challenges and multidisciplinary guidelines for optimal management of this group have recently been published<sup>102</sup>. Data from the POSH<sup>103</sup> cohort study have shown that in the absence of a known pathogenic germline mutation, there is no survival advantage from mastectomy compared with BCS.

Research is required to explore how concerns specific to young women should be managed. These include issues relating to fertility, bone health, consequences of extended endocrine therapy, and the psychological impact of a breast cancer diagnosis not only on the patient, but also their partners and family. Indications for germline mutation testing remain to be defined and the probability threshold for testing in the UK has recently been decreased from 20% to 10%. The surgeon has an important role in engaging with clinical geneticists and other collaborators to answer these key questions.

### **Pregnancy associated breast cancer**

Pregnancy-associated breast cancer (PABC) is estimated to affect 2.4-7.8 women per 100,000 live births. Two large on-going studies in the UK and Europe<sup>104 105</sup> will explore the incidence and short-term outcomes of PABC. Surgeons working in collaboration with obstetricians are ideally placed to recruit patients to relevant studies.

### **Older women**

The management of women with breast cancer diagnosed over the age of 70 years varies widely across the UK<sup>106-108</sup>, and is currently the subject of a national audit<sup>51</sup>. Older patients are more likely to be managed with primary endocrine therapy without surgery. Although several randomised trials have shown overall survival to be similar to combined surgery and adjuvant endocrine therapy, a Cochrane Review revealed that local control was significantly worse in the absence of surgical treatment<sup>109</sup>. Furthermore, those offered surgery are more likely to undergo mastectomy without the potential benefit of downstaging from neoadjuvant therapies and axillary management is more likely to be non-guideline compliant in older patients.

Whilst adjuvant chemotherapy is widely employed in younger women, usage is more selective and variable in patients over 70 years<sup>110</sup>. Failure to include older patients in clinical trials and tendencies to overestimate comorbidity and frailty whilst underestimating therapeutic benefit collectively influence treatment recommendations in the older patient.

Randomised trials to address these questions have failed to recruit for several reasons including lack of equipoise on the part of both clinician and patient<sup>111</sup>. However, both cohort<sup>112</sup> and qualitative studies<sup>113</sup> investigating factors which influence patient choice and evaluate interventions to reduce treatment variation have been more successful.

### **Male breast cancer**

Male breast cancer represents 0.5–1% of all breast cancers and has been understudied, with management decisions often extrapolated from studies of female breast cancer. This may be inappropriate as recent evidence suggests that these cancers may be biologically different. The majority of men with breast cancer will undergo primary surgery, and surgeons have a central role in recruiting these patients to on-going studies and promoting tissue collection for research.

## **RESEARCH METHODOLOGY**

## **Multidisciplinary collaboration**

Clinical research is multidisciplinary based and continued collaboration between breast surgeons and other disciplines is essential for ensuring advances in breast cancer research across the globe. Surgeons play roles as research leaders within their own areas of expertise, and are vital as collaborators within research teams. There is clear evidence of a changing culture and attitude in breast surgery in the UK with annual ABS Multidisciplinary Meetings bringing together experts to debate controversial topics and an increasingly visible surgical presence within national multidisciplinary research infrastructure such as the National Cancer Research Institute (NCRI) Breast Clinical Studies Group and the UK Breast Intergroup creating an environment where such collaborations can flourish. Consolidating and building on these successes will be crucial to increase research capacity and facilitate delivery of well-designed research to address gaps highlighted in this review.

## **Patient and public involvement**

Patient and public involvement is central to the delivery of high-quality research and patients are key to any successful multidisciplinary collaboration. Patients should be involved in the design, development and delivery of studies to ensure that research is relevant and addresses questions with clear patient focussed outcomes. Shared decision making approaches to breast cancer treatment should be explored in clinical trials. With inclusion of patient reported outcomes as standard. Breast cancer survivorship and secondary prevention are discussed in detail in the BCC gap analysis<sup>4</sup>. As surgeons have a significant role in the follow-up and ongoing management of patients with breast cancer they are well placed to work with patients to deliver research in these areas.

## **Clinical research**

The surgeon is well placed to synthesise current evidence, formulate new hypotheses, identify and question inconsistencies in current approaches, and to help design and develop innovative clinical trials. The surgeon is central to patient recruitment, monitoring and sample collection and represents a key link between patient and translational scientist. Surgeons are responsible for the diagnostic process and are involved in treatment planning for most breast cancer patients, and thus are key to recruitment to biological studies in the perioperative period which are increasingly important in the development of stratified medicine. Surgeons are usually trusted for advice and information and need to be enthusiastic

advocates of clinical trials; ensuring patients have full and equal access to information and participation in clinical research studies.

Although well-designed, pragmatic randomised trials are considered the 'gold standard' for determining efficacy, they may not be possible in some areas including assessment of radiotherapy effects on breast reconstruction, risk-reducing surgery or in certain groups such as older patients. In these settings, prospective cohort studies may be a reasonable alternative with rapid creation of large and powerful datasets which allow hypotheses to be explored and key questions addressed. The trainee research collaborative model has emerged as a successful cost-effective way of conducting these types of studies. Engaging trainees also has the potential to augment research capacity by fostering a new generation of surgeons with an understanding of research methodology, patient and public involvement and engagement in trial recruitment<sup>114-116</sup>. The success of this approach has recently been evidenced by a trainee-delivered prospective audit evaluating current practice with respect to resection margins<sup>117</sup>. Collaboration with psychosocial and qualitative researchers may allow surgeons to develop studies to explore issues around topics such as risk-reducing mastectomy and CPM. Health economic participation is vital, for evaluation of emerging technologies and devices, as favourable cost-effectiveness data will support commissioning of future service provision.

### **Translational research**

As acknowledged in the BCC gap analysis<sup>4</sup>, improved collection of tumour samples and blood from patients at all disease stages is essential for the ongoing development of personalised medicine. A culture change allowing routine collection and biobanking of samples at diagnosis and during treatment is urgently required. Consensus is required to optimise sample collection and preanalytical processing, allowing the assessment of fresh and formalin-fixed paraffin embedded samples appropriate for "omics" studies as well as techniques such as individualised cell culture analysis, single cell sequencing, and patient derived organotypic models and xenografts<sup>4</sup>.

Identification and validation of biomarkers which predict for local or "surgical" disease endpoints will be critical in the context of developing stratified medicine. Engaging surgeons to routinely participate in tissue banking and translational studies is an essential prerequisite for progression of biomarker driven research.

## RESEARCH FUNDING

As highlighted above, currently only a small proportion of governmental research spend is directed towards surgical research. Recent investment in surgical research infrastructure such as the Royal College of Surgeons Surgical Trials Initiative which in partnership with the National Institute of Health Research (NIHR), the professional associations and charitable funders including Cancer Research UK and Breast Cancer Now has created a network of surgical trials units and Surgical Speciality Leads to increase the quality and number of surgical trials in the UK. This drive to place research at the centre of surgical culture includes increasing research capacity through developing existing clinical research networks, as well as in the training of current and future generations of surgeons in research methodology and Good Clinical Practice to ensure the high quality of future studies. The success of this initiative has already been demonstrated with a portfolio of 85 trials recruiting over 25,000 patients across 10 different specialities in the four years since inception<sup>118</sup>.

Further funding, however, will be needed and funding bodies responsible for supporting surgical and breast cancer research in the UK need to be cognisant that addressing the critical gaps in clinical and translation research outlined in this analysis will require significant investment over the next two decades to benefit patients, clinicians and healthcare providers. It is anticipated that as surgeons continue to embrace 'team science' by developing their multidisciplinary collaborations and building strong links with methodologists, the funding successes seen in surgically-led studies such as LORIS, POSNOC and SMALL will continue increase leading to well-designed and conducted studies that address these issues.

## CONCLUSIONS

Surgeons are uniquely placed to design and deliver studies addressing the key gaps in our knowledge of breast cancer management. Historically, surgeons have played key roles in improving breast cancer outcomes, far beyond evolution of surgical techniques. The concept of 'surgical' research being restricted to devices or techniques is outdated and should reflect the spectrum of roles that surgeons have in contemporary multidisciplinary research. Evolving research platforms such as 'window of opportunity' studies and trainee collaboratives offer surgeons unrivalled opportunities to develop more

effective treatments, reduce overtreatment, and become involved in research. Open multidisciplinary collaboration will be vital to ensure progress in breast cancer research from an international perspective.

The key research gaps identified in this analysis are summarised in table 1 and include issues surrounding overdiagnosis and overtreatment, the selection of patients for neoadjuvant therapies and their subsequent surgical management and refining surgical techniques to improve re-operation rates in women having breast conserving surgery. Evidence should be generated to enable stratification, personalisation (patient selection criteria, the impact of adjuvant treatments and co-morbidities) and clinical and cost-effectiveness of breast reconstruction, including mechanisms for the evaluation of novel technologies and surgical approaches. Management pathways for the axilla should be further clarified particularly in the context of post-neoadjuvant treatment and the indications for risk-reducing surgery and contralateral prophylactic mastectomy should be more clearly defined and standardised.

Proposed strategic solutions to address these gaps include the integration of a research culture into surgical practice at all stages of training with breast surgeons becoming key proponents of scientific, translational and clinical research and the development of surgical leadership in design and delivery of clinical research. Surgical clinician scientists should be nurtured to accelerate translational research to address key surgical and clinical questions and an agreed framework for biobanking of clinical samples at key points in the patient treatment pathway should be developed to facilitate translational research studies. Finally there should be further development and optimisation of clinical trial methodologies relevant to address key surgical questions in breast cancer management.

High-quality research is essential to improve patient outcomes and should be embedded in surgical culture to engage and empower surgeons to participate in trials for the benefit of their patients. All surgeons should offer their patients the opportunity to enter well-designed trials, and research should remain at the heart of breast surgical practice.





## **Collaborators**

### **Author contributions**

RIC and MWR conceived the project; AG, SP, CCK, JH, AF, ARC, PF, RIC and RV were section leads and co-ordinated expert input; SP produced the first draft of the manuscript; RIC, SMcl, MWR and JB critically revised the manuscript; all authors reviewed and approved the manuscript prior to submission.

### **The Association of Breast Surgery Gap Analysis Working Group (in alphabetical order) are:**

Narendra Nath Basu; John Benson; Nigel J Bundred; Amtul R Carmichael; Nathan Coombs; Ramsey I Cutress; John Dickson; J Michael Dixon; Michael Douek; Patricia Fairbrother; Adele Francis; Amit Goyal; Diana Harcourt; James Harvey; Chris Holcombe; Jonathan Horsnell; Fahad M Iqbal; Lucy R Khan; Cliona C Kirwan; Daniel R Leff; Anthony J Maxwell; Stuart A McIntosh; Nicole Paraskeva; Shelley Potter; Tim Rattay; Malcolm W Reed; Amtul S Sami; Julian Singer; Edward R St John; Ash Subramanian; Jeffrey S Tobias; Nader Touqan; Jayant S Vaidya; Raghavan Vidya, Zoe E Winters.

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